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Quinolone resistance of gram negative bacteria from the patients with malignancies and relationship with prophylaxis

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Abstract

Fluoroquinolones are the most commonly used antibiotics for the treatment and prophylaxis of patients with malignancies. But resistance development is a big problem.With the aim of identifying the epidemiological data about the local fluoroquinolone resistance of the patients with malignancies followed up in the hospital or on outpatient basis, fluoroquinolone resistance of gram negative bacteria isolated from different materials of these patients was investigated. In our hospital, from January 2013 to August 2014, gram negative isolates that were isolated from the samples of patients with malignancies followed-up by Hematology and Oncology Departments were retrospectively analyzed. Within a period of one and a half years, 227 Gram negative bacteria were isolated from the materials of the patients hospitalized in our hospital. Quinolone resistance rates were 63% for E.coli, 49% for Klebsiella pneumoniae, 34% for Pseudomonas aeruginosa, 72% for Acinetobacter baumannii , with a mean of 52% for all Gram negatives. When patients who received and who did not receive quinolone prophylaxis were compared, resistance rate was 57% (26/61) for those receiving prophylaxis and 50 %(83/166) for those who did not. In conclusion, fluoroquinolone resistance rates were considerably high and it was higher in the patients who received quinolone prophylaxis, but it wasn't statistically significant. In the oral treatment of febrile neutropenic patients, empirical treatment aims at Gram negative pathogens and considers quinolones as the first choice; however this data raises a suspicion about the efficacy and adequacy of quinolones.

Key words: Quinolone resistance, gram negative bacteria, malignancy patients, quinolone prophylaxis

Introduction

Febrile neutropenia that develops in Hematology-Oncology patients generally requires hospitalization and is the most common complication that has a fatal course. Until its cause is declared, it is regarded as infection related and necessitates urgent antibiotic treatment. Based on different clinical evaluation scoring criteria, if the patients are hospitalized, *Pseudomonas* is primarily targeted and treatment is initiated with wide spectrum antibiotics having antipseudomonal activity. The patients can as well be treated as an outpatient receiving oral quinolone antibiotherapy aimed at possible Gram negative pathogens. Fluoroquinolones are the most commonly used group of antibiotics for the treatment of malignancy patients on outpatient basis and for the prophylaxis of neutropenic patients aiming at Gram negative bacteria. Neutropenia is usually defined as an absolute neutrophil count (ANC) <1500 cells/µL, and severe neutropenia is usually defined as an ANC< 500 cells/µL or an ANC that is expected to decrease to < 500 cells/µL over the next 48 hours [1,2]The risk of clinically important infection rises as the neutrophil count falls below 500 cells/µL and is higher in those with a prolonged duration of neutropenia (>7 days). High risk patients as those who are expected to be neutropenic for >7 days [1]. Antimicrobial prophylaxis involves the administration of an antimicrobial drug to prevent neutropenic fever and infectious complications in patients at increased risk. Antibacterial prophylactic regimens target *Pseudomonas aeruginosa* and other gram negative bacilli, since the pathogens are particularly virulent and may cause life-threatening infections. Guidelines from the Infectious Disease Society of America (IDSA) recommend consideration of fluoroquinolone prophylaxis in patients at high risk for profound prolonged neutropenia [1]. Quinolone prophylaxis used for cancer patients is beneficial as it decreases the incidence of bacterial infections and mortality [3-6]. However, this practice results in an increase in quinolone resistance [3,4]. At institutions that use fluoroquinolone prophylaxis, monitoring of the prevalance of fluoroquinolone resistance among gram negative bacilli should be performed.

To this end, different clinical materials from malignancy patients followed-up in our hospital were analyzed for the fluoroquinolone resistance of the isolated pathogenic

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bacteria. Furthermore, quinolone resistance of the isolates growing in the cultures of patients who received and who did not receive quinolone prophylaxis was also compared.

Materials and methods

We conducted an observational retrospective study at two hospitals of Bilim University, Istanbul, Turkey. These are tertiary care hospitals with 275 beds totally, including a hematology and hematopoietic cell transplant unit with 18 single-bed rooms with high efficiency particulate air (HEPA) filter and positive pressure, and 25 single-bed rooms without hepa filter. In our hospitals which either hospitalize Hematology-Oncology patients or follow them up on outpatient basis. In the period from January 2013 to August 2014, Gram negative isolates growing in the culture specimens of the malignancy patients as infection agent who were either hospitalized or followed up on outpatient basis were retrospectively analyzed. The patients age, gender, malignant disease of the patient, condition of quinolone prophylaxis, isolated gram negative bacteria, material of the isolation, ciprofloxacin susceptibility of the bacteria were recorded. Samples of urine, sputum, wound, abscess, were inoculated onto 5% sheep blood agar, or chocolate agar and Mac Conkey agar (bioMerieux) .For blood cultures, BacT/ALERT 3D (BioMerieux, France) system that detects growth with signals was used. The identification of bacteria and their antibiotic susceptibility was carried out with VITEK 2 (bioMerieux, France) automated system [7].

In our hospitals, all the patients with hematological malignancies or solid organ tumors with an expected duration of neutropenia over 7 days and who do not have a contraindication to receiving a quinolone, receives prophylaxis with fluoroquinolones.

Statistical analysis:

For the comparisons of groups, pearson Chi-square and Fisher exact tests were used. In the evaluation of the possible effects of the risk factors, logistic regression analysis methods were employed. p value < 0.05 was considered statistically significant.

Results

O Mean age of the patients included in the study was 61 years (range: 25-86 years). Sixty-nine percent of the patients were male (n: 157) and 31% were female (n: 70), 137 (60%) patients had hematological malignancies and 90 (40%) had solid organ tumors.

From the patients with malignancies hospitalized during the period of one and a half years, 227 Gram negative bacteria were isolated from different type of materials and from different patients. Of these isolates, 92 were isolated from blood, 78 from urine, 15 from wound swaps, 14 from tracheostomy, 13 from sputum, 11 drains, 2 from bronchoalveolar lavage fluid, 1 from cerebrospinal fluid and finally 1 from ascites fluid. As for the bacteria, 111(48,8%) were *E.coli*, 37(16,2%) were *Klebsiella pneumoniae spp*., 33(14,5%) were *Pseudomonas aeruginosa*, 18(7,9%) were *Acinetobacter baumannii*, 7(3%) were *Proteus spp*., 5(2,2%) were *Enterobacter*, 5(2,2%) were *Serratia spp*., 4(1,8%) were *Klebsiella oxytoca*, 2(0,9%) were *Stenotrophomonas maltophilia*, 2(0,9%) were *Citrobacter spp*., 2(0,9%) were *Morganella spp* and 1(0,5%) was *Sphingomonas paucimobilis* as shown in table 1. Quinolone resistance rates were 63% for *E.coli*, 49% for *Klebsiella pneumoniae*, 34% for *Pseudomonas aeruginosa*, 72% for *Acinetobacter baumannii* respectively and a mean sensitivity rate of 52% for all Gram negative bacteria as shown in table 2. When the patients were divided as hematology patients and oncology patients, the resistance rate was higher among hematology patients with 58% and was 46% for oncology patients. When patients who received and who did not receive quinolone prophylaxis were compared, resistance rate was 57% (26/61) for those receiving prophylaxis while being 50% (83/166) for those who did not receive prophylaxis. But the difference between two groups is not statistically significant. (P=0,32) Among hematology patients, the ratio of patients receiving quinolone prophylaxis was 36 %(49/137), among oncology patients this ratio was 13% (12/90).

Table 1. Distrubition of the isolated gram negative bacteria

BACTERIA	Number	%
E.coli	111	49
Klebsiella pneumoniae spp.	37	16
Pseudomonas aeruginosa	33	15
Acinetobacter baumannii	18	8
Proteus spp.	7	3
Enterobacter spp.	5	2,2
Serratia spp	5	2,2
Klebsiella oxytoca	4	1,8
Stenotrophomonas maltophilia	2	0,8
Citrobacter	2	0,8
Morganella	2	0,8
Sphingomonas paucimobilis	1	0,4
TOTAL	227	100

Table 2. Floroquinolone resistance rates of the isolated bacteria

BACTERIA	Floroquinolone resistance rates (%)
E.coli	63
Klebsiella pn spp.	49
Pseudomonas spp.	34
Acinetobacter spp.	72
mean resistance rate	52
Resistance rates for Quinolone receivers	57
Resistance rates for Quinolone non-receivers	50

Discussion

From 2007 to date, the rate of Gram negative bacteria recovery ranged from 24.7 to 75.8 % in cancer patients cohorts [8]. E.coli represented the most common species (32%), followed by *Pseudomonas aeroginosa* (20.1%) [8].We found similar rates, the most common isolate was *E.coli* (48,8%) but *Klebsiella* isolates (16,2%) were more common than *Pseudomonas* isolates (14,5%) according to our results.

During recent years, quinolones are used in a widespread manner for the treatment of infections caused by Gram negative bacteria like *E.coli*. However, quinolone resistance is demonstrating a rapid increase among these strains [4].After quinolones were introduced in clinical practice, they have excellent activity against a wide range of pathogens including enteric Gram-negative bacilli and *Pseudomonas*. For that reason quinolones became the ideal drug for use in prophylaxis and treatment of febril neutropenic patients. But widespread use of quinolones for prophylaxis and treatment caused resistance problem [9].

Today, quinolone resistance is seen in 33-50% of *E.coli* isolates and 13-20% of, *Klebsiella* isolates [10]. In a study by Cattaneo et al., quinolone resistance was reported as the most frequently seen type of resistance, they said that it developed in 56% of the bacterial isolates. Moreover, quinolone resistant *E.coli* isolates constituted 20% of all the isolates and 87% of the *E.coli* isolates [11]. In a study by Trecarichi et al., quinolone resistance of gram negative bacteria in febrile neutropenic patients with cancer, quinolone susceptibility of *E.coli* isolates were ranging from 14.9% to 66.7% (mean 47.2%); for *Klebsiella pneumoniae* isolates from 28.5% to 98.7% (mean 61.1%), for *Pseudomonas* isolates 18% to 94% (mean 51.6%), for *Acinetobacter* isolates 58.1% [8]. When the source of bacteriemia was investigated in febrile neutropenia patients, fluoroquinolone resistance of *E.coli* was reported as being 0-35%. The administration of quinolone prophylaxis and frequent use of quinolones is reported to contribute to this increase in the resistance [12].

Based on the data from a 14-year long surveillance study by Schelenz et al. at an Oncology-Hematology Center in the UK, ciprofloxacin resistance of Gram negative isolates was 22% among hematology patients and 5% among oncology patients. Hematology patients had a higher rate of ciprofloxacin use than oncology patients and the use of ciprofloxacin further contributed to the increase in resistance [13].

When we look at the studies reported from our country, Hamidi et al. focused on the agents of bacteriemia in febrile neutropenia patients. They investigated 45 bacteremia episodes of 37 patients and reported the quinolone resistance 75% for *E.coli* and 57% for *Klebsiella pneumonia* [14]. In another study by Tunçcan et al., ciprofloxacin resistance of *E.col*i isolates isolated from blood cultures of patients with hematological malignancies was reported as 58% [15]. Yurtsever et al. reported a ciprofloxacin resistance rate of 76% for *E.coli* (n:62) isolated from blood cultures of febrile neutropenia patients [16].

In our study, the resistance rates we identified were similar to studies reported from our country, 63% for E.coli, 49% for Klebsiella pneumoniae spp, 34% for Pseudomonas, and 72% for Acinetobacter with a mean resistance rate of 52% for all Gram negatives. When the patients were divided as hematology patients and oncology patients, the resistance rate was higher among hematology patients with 58% and was 46% for oncology patients. When the use of ciprofloxacin for prophylaxis was investigated, the rates were 36% for hematology patients and 13% for oncology patients being higher among hematology patients. When patients who received and who did not receive quinolone prophylaxis were compared, resistance rate was 57% (26/61) for those receiving prophylaxis while being 50% (83/166) for those who did not receive prophylaxis. Firstly we thought that higher rate of quinolone prophylaxis among hematology patients results in an increase in quinolone resistance. But according to statistically analysis the difference between two groups is not statistically significant in our study. Maybe when the number of cases increase, it may cause statistically significant results.

In conclusion, due to the frequent use of fluoroquinolones in empirical treatment and prophylaxis, resistance rates are significantly high; quinolone prophylaxis is thought to increase quinolone resistance. As concerns the oral treatment for febrile neutropenia patients aiming at Gram negative pathogens, quinolones are considered as the first option in empirical treatment. However, as the use of quinolones increase, the resistance rates might as well increase leading to a suspicion in their efficacy and adequacy .Widespread

use of floroquinolones may reduce prophylaxis and treatment efficacy in neutropenic cancer patients.

Disclosure:

The authors report no conflicts of interest in this work.

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